WPSC
Wood Preservative Science Council

Approaches to Cancer Risk Assessment:
Considerations for Dose Response Assessment in Relation to Inorganic Arsenic

Comments to the Science Advisory Board, Arsenic Review Panel
February 17, 2006

INTRODUCTION

Risk assessment is the process of organizing and analyzing information to determine if a chemical might cause harm to exposed people or populations. The risk assessment process consists of four primary steps: hazard assessment, dose-response assessment, exposure assessment, and risk characterization. In the case of inorganic arsenic, it has been well-established, in the hazard assessment step, that it is carcinogenic to humans at high doses. The next critical step, that of dose-response assessment, is currently under consideration by US-EPA with the advice of the Science Advisory Board Arsenic Review Panel.

Dose-response assessment for inorganic arsenic is complicated by the divergence of opinion in interpreting the epidemiology data as well as the mode of action data, all of which support a threshold phenomenon. EPA's Guidelines for Carcinogen Risk Assessment allow for the use of scientific judgment and support the use of a non-linear model if , as in the case of inorganic arsenic, the data support a non-linear dose response and threshold responses.

US-EPA's Guidelines for Carcinogen Risk Assessment were updated in 2005 and can be found at http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=116283. The main document is "Guidelines for Carcinogen Risk Assessment" EPA/630/P-03/001F, March 2005. Supplemental guidance and multiple explanatory items also are available.

GUIDELINES ARE NOT REGULATORY MANDATES

As identified by EPA, "The Guidelines provide a framework to EPA scientists for assessing possible cancer risks from exposures to pollutants or other agents in the environment. They will also inform Agency decision makers and the public about these recommended procedures. Revisions to the Cancer Guidelines are intended to make greater use of the increasing scientific understanding of processes of cancer development." Importantly, EPA clearly identifies that these guidelines are recommendations with the ability for flexibility when justified by the science.

In fact, EPA states[1] "These cancer guidelines are intended as guidance only. They do not establish any substantive "rules" under the Administrative Procedure Act or any other law

[1] US Environmental Protection Agency, Risk Assessment Forum. Guidelines for Carcinogen Risk Assessment" EPA/630/P-03/001F, March 2005, page 1-2.

P.O. Box 183 | Manakin-Sabot, VA 23103 | Ph 804.749.8016 | Fax 804.749.8017
www.woodpreservativescience.org

and have no binding effect on EPA or any regulated entity, but instead represent a non-binding statement of policy."

GUIDANCE FOR DOSE-RESPONSE ASSESSMENT

Dose-response assessment is a two-step process. First, the available data need to be carefully considered and modeled, taking into account all available data and scientific judgment. It is only when that step is completed that the second step comes into consideration. The second step of dose-response assessment is to predict (extrapolate) the potential response when there are no observable data in the range of human exposure. In some cases, the scientific evidence supports the use of extrapolation below the observable range; in other cases, a reference dose/reference concentration will be used. However, when observable data are within the range of human exposure, there is no need to extrapolate below those levels to predict the potential response. Instead, all observed data should be considered in an appropriate model.

EPA's Guidance provides a framework for conducting dose-response assessments and allows significant flexibility in how those assessments are performed, based on the available scientific data, biological information, and on a weight of scientific evidence approach.

The Guidelines identify that dose-response analysis is a complex process[2]:

> "A dose-response analysis is generally developed from each study that reports quantitative data on dose and response. Alternative measures of dose are available for analyzing human and animal studies (see Section 3.1). A two-step approach distinguishes analysis of the dose-response data from inferences made about lower doses. The first step is an analysis of dose and response in the range of observation of the experimental or epidemiologic studies (see Section 3.2). Modeling is encouraged to incorporate a wide range of experimental data into the dose-response assessment (see Sections 3.1.2, 3.2.1, 3.2.2, 3.2.3). The modeling yields a point of departure (POD) near the lower end of the observed range, without significant extrapolation to lower doses (see Sections 3.2.4, 3.2.5). The second step is extrapolation to lower doses (see Section 3.3). The extrapolation approach considers what is known about the agent's mode of action (see Section 3.3.1). Both linear and nonlinear approaches are available (see Sections 3.3.3, 3.3.4). When multiple estimates can be developed, the strengths and weaknesses of each are presented."

The use of epidemiologic data is discussed extensively, both in terms of hazard assessment, i.e., determination of causality, but also in terms of the preferred use of such data in determining the dose-response assessment. Clearly, epidemiologic data provide data within the range of human exposures, obviating the need for extrapolation to such ranges, and provide extensive information on the exposure assessment component. In particular, analytical studies (such as case-control and cohort designs) provide the best basis for identifying a causal association between exposure and cancer and in characterizing the exposure component[3]. Ecological studies are unable to establish the association because of a lack of data on the degree of exposure. Such studies are useful, however, for other purposes such as identifying patterns and trends.

---

[2] Ibid at page 3-1.

[3] Ibid at pages 2-3 to 2-11.

Evaluation Within the Range of Observed Data

The Guidelines provide an extensive discussion of how to evaluate data which are within the range of observation and recommendations on how to address potential exposures which are below the range of observation. In particular, Section 3.2.1[4] discusses the use of epidemiologic data, meta-analyses, and potential considerations in using epidemiologic data (such as bias due to comparison populations that are not free from exposure). The Guidelines clearly support the use of epidemiologic studies, stating "Ideally, epidemiologic data would be used to select the dose-response function for human exposure."[5] Clearly the questions of exposure come into consideration. When the range of exposure is small, it is more difficult to clearly identify the shape of the dose-response curve. In the case of inorganic arsenic, however, the range of exposure across studies is very broad and allows for better identification of the dose-response curve. The Guidelines identify that a linear model is typically used, unless the fit to the observed data is poor. Under those circumstances, the Guidelines clearly recommend consideration of other and more flexible models.

The Guidelines support the use of all available data and the use of appropriate techniques to improve precision:[6]

> "When several studies are available for dose-response analysis, *meta-analysis* can provide a systematic approach to weighing positive studies and those studies that do not show positive results, and calculating an overall risk estimate with greater precision. Issues considered include the comparability of studies, heterogeneity across studies, and the potential for a single large study to dominate the analysis. Confidence in a meta-analysis is increased when it considers study quality, including definition of the study population and comparison group, measurement of exposure, potential for exposure misclassification, adequacy of follow-up period, and analysis of confounders."

Clearly, the Guidelines do not demand a linear model be applied using a single study when extensive additional data are available and useful to better characterize the dose-response curve.

Extrapolation Below the Range of Observed Data

It is only when exposures occur below the range of observed data available in experimental data (including epidemiologic studies) where it may become necessary to extrapolate to lower dose levels in order to characterize the potential risk. Section 3.2.4 of the Guidelines discusses Point of Departure (POD), where the POD is "an estimated dose (expressed in human-equivalent terms) near the lower end of the observed range without significant extrapolation to lower doses."[7] The Guidelines identify that careful analysis of the available

---

[4] Ibid at pages 3-11 to 3-13.

[5] Ibid at page 3-11

[6] Ibid at page 3-13

[7] Ibid at page 3-16.

data are needed to estimate the POD but that the POD must be supported by data in the observed range.

The Guidelines state[8] that "(t)he purpose of low-dose extrapolation is to provide as much information as possible about risk in the range of doses below the observed data." It should be emphasized that low-dose extrapolation is only below the POD, which itself is determined based on the available and observed data. In considering what extrapolation model is appropriate for data which are below the observed range, the Guidelines suggest that a linear extrapolation is appropriate when mode of action data clearly suggest a linear response below the POD. As a default, health-protective approach, a linear extrapolation also is recommended[9] "(w)hen the weight of evidence evaluation of all available data are insufficient to establish the mode of action for a tumor site ***and*** when scientifically plausible based on the available data...." (emphasis added). In the latter cases[10], "(f)or linear extrapolation, a line should be drawn from the POD to the origin, corrected for background." EPA notes, however, that the dose-response curve generally is not linear at higher doses when linear extrapolation is used to model a low-dose response below the range of observed data. However, nonlinear extrapolations below the POD also can be considered, even when a clear mode of action, as in the case of inorganic arsenic, is unknown. This is appropriate when available data and a weight of evidence evaluation support a nonlinear approach[11].

In fact, the only time extrapolation is used is to address potential risks that are outside the observed range of data (below the POD). The use of any single model across the range of both observed and below observed data would be highly unusual and inconsistent with the Guidelines particularly when doing so would be inconsistent with the observed data.

The key objective for low-dose extrapolation is provide information about risk in the range of doses below the observed data. In the case of inorganic arsenic, the use of the low dose range human exposure data may obviate the need for low dose extrapolation. For characterization of risk at levels below even those reported, a safety evaluation approach may be more appropriate, using the Margin of Exposure approach.

CONCLUSION

Consideration of the appropriate dose response approach must be based on the available data and cannot be just the application of a mathematical model. Risk characterization, which is the end result of the hazard, dose-response, and exposure assessments, "...common sense, reasonable applications of assumptions and policy, and transparency are essential to avoid unrealistically high estimates."[12] As proposed by the Office of Management and Budget, Office of Information and Regulatory Affairs, standards for risk

---

[8] Ibid at page 3-20.

[9] Ibid at page 3-21.

[10] Ibid at page 3-23.

[11] Ibid at page 3-23 to 3-24.

[12] Ibid at page 5-3.

assessments conducted by the Federal Government should meet certain quality standards[13]. In particular, in relation to the use of models in risk assessment, OMB identifies that dose-response models are important in characterizing potentials risks at low doses ("i.e., doses below the range of empirical detection of cancer risk)" but further identifies that the use of a non-linear dose response is fully appropriate when available epidemiologic or biologic data demonstrate that the response is not linear.[14]

There is no requirement in EPA's Guidelines which would mandate the use of a default linear model across the full range of observed data and extrapolation below that range, regardless of whether a clear mode of action has been identified. In fact, the use of such a model clearly is discouraged by the Guidelines when extensive data for inorganic arsenic clearly identify a nonlinear dose response. EPA's Guidelines provide a flexible approach to the assessment of the dose-response curve for a carcinogenic agent but clearly support the use of multiple approaches, weight of scientific evidence and full consideration of all available data.

The Science Advisory Board Arsenic Review Panel should consider alternative approaches to linear extrapolation for inorganic arsenic, as is clearly provided for within EPA's Risk Assessment Guidelines.

Respectfully submitted,

Jim Hale
Executive Director
WPSC

[13] Proposed Risk Assessment Bulletin, January 9, 2006.
http://www.whitehouse.gov/omb/inforeg/proposed_risk_assessment_bulletin_010906.pdf

[14] Ibid at page 18.